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L2   ANSWER 1 OF 28  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2004:266901  CAPLUS
DN   140:302341
TI   Protein complexes of the tumor necrosis factor-α signalling pathway
     for diagnosis, therapy and drug screening
IN   Bouwmeester, Tewis; Huhse, Bettina; Bauch, Angela; Ruffner, Heinz; Bauer,
     Andreas; Kruse, Ulrich; Kuester, Bernhard; Superti-Furga, Guilio
PA   Cellzome Ag, Germany
SO   Eur. Pat. Appl., 549 pp.
     CODEN: EPXXDW
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   EP 1403282           A1     20040331    EP 2002-21809           20020926
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
     WO 2004035783         A2     20040429    WO 2003-EP50655         20030924
     WO 2004035783         C2     20040930
     WO 2004035783         A3     20041111
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
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         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI EP 2002-21809         A      20020926
     EP 2003-100274        A      20030210
AB   The present invention relates to protein complexes of the Tumor necrosis
     factor-α-signaling pathway, component proteins of said complexes,
     fragments and derivs. of the component proteins and antibodies specific to
     the complexes.  The present invention also relates to methods for use of
     the complexes of the TNF-α-signaling pathway and their interaction
     in screening, diagnosis and therapy as well to methods of preparing the
     complexes.  Pharmaceutical compns. comprising the protein complexes and
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antibodies specific to the complexes are especially useful for diagnosis and treatment of inflammation, infection, neurodegenerative disease and cancer.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 28 MEDLINE on STN DUPLICATE 1
AN 2004417047 MEDLINE
DN PubMed ID: 15218018
TI Activation mechanism of c-Jun amino-terminal kinase in the course of neural differentiation of P19 embryonic carcinoma cells.
AU Akiyama Shoko; Yonezawa Takayuki; Kudo Tada-Aki; Li Ming Guang; Wang Hong; Ito Michihiko; Yoshioka Katsuji; Ninomiya-Tsuji Jun; Matsumoto Kunihiro; Kanamaru Ryunosuke; Tamura Shinri; Kobayashi Takayasu
CS Departments of Biochemistry and Clinical Oncology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan.
SO Journal of biological chemistry, (2004 Aug 27) 279 (35) 36616-20.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200410
ED Entered STN: 20040824
Last Updated on STN: 20041007
Entered Medline: 20041006
AB P19 embryonic carcinoma cells, a model system for studying early development and differentiation, can differentiate into neurons and primitive endoderm-like cells depending on the culture conditions. We have previously reported that the activation of c-Jun amino-terminal kinase (JNK) is required for the retinoic acid-induced neural differentiation of P19 cells. However, the signaling pathway(s) responsible for the activation of JNK has not been known. In this study, we demonstrated that activities of MAPK kinase 4 (MKK4) and TAK1, one of the upstream kinases of MKK4, were enhanced in the neurally differentiating cells. Inhibition of the neural differentiation by an overexpression of protein phosphatase 2Cepsilon, an inactivator of TAK1, suggested a critical role of the TAK1 signaling pathway during the differentiation. Confocal microscopic analysis indicated that TAK1, phospho-MKK4, and phospho-JNK were colocalized with tubulin in the neurites and localized also in the nuclei of the differentiating cells. In contrast, two **TAK1-binding** proteins, **TAB1** and TAB2, which are involved in the activation of TAK1, were localized in the neurites and the nuclei of the differentiating cells, respectively. These results suggest that two distinct TAK1-MKK4-JNK signaling pathways are independently activated at the different intracellular locations and may participate in the regulation of the neural differentiation of P19 cells.

L2 ANSWER 3 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:230393 CAPLUS
DN 140:352540
TI TAB3, a new binding partner of the protein kinase TAK1
AU Cheung, Peter C. F.; Nebreda, Angel R.; Cohen, Philip
CS MRC Protein Phosphorylation Unit, School of Life Sciences, University of Dundee, Dundee, DD1 5EH, UK
SO Biochemical Journal (2004), 378(1), 27-34
CODEN: BIJOAK; ISSN: 0264-6021
PB Portland Press Ltd.
DT Journal
LA English
AB We have identified a new binding partner of the TGFβ (transforming growth factor-β)-activated protein kinase (TAK1), termed TAB3

(TAK1-binding protein-3), which shares 48% amino acid sequence identity with TAB2. Our results indicate that two distinct TAK1 complexes are present in cells. One comprises TAK1 complexed with TAB1 and TAB2, and the other TAK1 complexed with TAB1 and TAB3. Both complexes are activated in response to tumor necrosis factor-α or interleukin-1 in human epithelial KB cells or bacterial lipopolysaccharide in RAW264.7 macrophages, and are subject to feedback control by stress-activated protein kinase 2a (SAPK2a; also called p38α). The electrophoretic mobility of TAB2 and TAB3 decreases in response to these agonists or osmotic shock, and is reversed by treatment with protein phosphatase-1. The decrease in mobility of TAB3 is prevented if the cells are incubated with SB 203580 before stimulation, but treatment with SB 203580 produces forms of TAB2 with a mobility intermediate between that observed for TAB2 in unstimulated and stimulated cells. Similar results were obtained in embryonic fibroblasts from mice deficient in SAPK2a/p38α. Our results indicate that TAB3 is phosphorylated via the SAPK2a/p38α pathway, whereas TAB2 is phosphorylated at two or more sites by both an SAPK2a/p38α-dependent and an SB 203580-independent kinase. The SAPK2a/p38α-mediated phosphorylation of TAB2 and TAB3 may contribute to the SAPK2a/p38α-mediated feedback control of TAK1 activity that also involves the phosphorylation of TAB1. We also show that the agonist-induced activation of TAK1 complexes requires the phosphorylation of the TAK1 catalytic subunit at a serine/threonine residue(s).

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L2 ANSWER 4 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:300523 CAPLUS
DN 138:314539
TI TRAF6-regulated IKK activators (TRIKA1 and TRIKA2) and their use as anti-inflammatory targets
IN Chen, Zhijian J.; Deng, Li
PA USA
SO U.S. Pat. Appl. Publ., 29 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003073097	A1	20030417	US 2001-76918	20011011
PRAI	US 2001-76918		20011011		

AB Proteins in the IKK and JNK signaling pathways, such as NFκB, are involved in the regulation of inflammatory diseases. Through phosphorylation and polyubiquitination, IκB proteins which sequester NFκB in the cytoplasm, are degraded by the ubiquitin-proteasome pathway releasing NFκB to the nucleus where it is activated. The present invention provides methods utilizing the composition of proteins in the IKK, JNK and ubiquitin-proteasome pathways such as, TRAF6 or TRAF2 (E3-ubiquitin protein ligase), TRIKA1/Uev1A/Ubc13 complex (E2-ubiquitin conjugating enzyme), and TRIKA2/TAK1(protein kinase), in screening for candidate modulators involved in activation of the IKK and JNK pathways. The application further provides methods of utilizing the candidate modulators as drug therapeutics against inflammatory and immune diseases.

L2 ANSWER 5 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:360779 CAPLUS
DN 138:380400
TI TAK1-TAB1 fusion protein: a novel constitutively active mitogen-activated protein kinase kinase kinase for use in drug screening
IN Sugita, Naohisa; Sakurai, Hiroaki; Sato, Naoya
PA Tanabe Seiyaku Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 34 pp.
CODEN: JKXXAF

DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2003135070	A2	20030513	JP 2001-335988	20011101
PRAI	JP 2001-335988		20011101		

AB A fusion protein comprising human transforming growth factor-β-activated kinase 1 (TAK1) N-terminal MAPKKK domain and human TAK1 **binding** protein 1 (**TAB1**) C-terminal **TAK1** activation domain, functional as active mutant TAK1, encoding cDNAs, recombinant expression, and use in screening TAK1 inhibitors, are disclosed. TAK1 and TAB1 are connect via a linker peptide. Activation of JNK, p38, or IKK, or induction of cytokine production, such as IL-6, IL-1, or TNF, may be assayed for screening. TAK1 mitogen-activated protein kinase kinase kinase (MAP3K) is activated by its specific activator, TAK1-binding protein 1 (TAB1). A constitutively active TAK1 mutant has not yet been generated due to the indispensable requirement of TAB1 for TAK1 kinase activity. In this study, the authors generated a novel constitutively active TAK1 by fusing its kinase domain to the minimal TAK1-activation domain of TAB1. Co-immunopptn. assay demonstrated that these domains interacted intra-molecularly. The TAK1-TAB1 fusion protein showed a significant MAP3K activity in vitro and activated c-Jun N-terminal kinase/p38 MAPKs and IκB kinase in vivo, which was followed by increased production of interleukin-6. These results indicate that the fusion protein is useful for characterizing the physiol. roles of the TAK1-TAB1 complex.

L2 ANSWER 6 OF 28 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003270179 EMBASE
TI TAB1β (transforming growth factor-β-activated protein kinase 1-binding protein 1β), a novel splicing variant of TAB1 that interacts with p38α but not TAK1.
AU Ge B.; Xiong X.; Jing Q.; Mosley J.L.; Filose A.; Bian D.; Huang S.; Han J.
CS J. Han, Dept. of Immunology, Scripps Research Institute, 10550 North Torrey Pines Rd., San Diego, CA 92037, United States. jhan@scripps.edu
SO Journal of Biological Chemistry, (24 Jan 2003) 278/4 (2286-2293).
Refs: 60
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB The mitogen-activated protein kinases (MAPKs) play an important role in a variety of biological processes. Activation of MAPKs is mediated by phosphorylation on specific regulatory tyrosine and threonine sites. We have recently found that activation of p38α MAPK can be carried out not only by its upstream MAPK kinases (MKKs) but also by p38α autophosphorylation. p38α autoactivation requires an interaction of p38α with TAB1 (transforming growth factor-β-activated protein kinase 1-binding protein 1). The autoactivation mechanism of p38α has been found to be important in cellular responses to a number of physiologically relevant stimuli. Here, we report the characterization of a splicing variant of TAB1, TAB1β. TAB1 and TABiβ share the first 10 exons. The 11th and 12th exons of TAB1 were spliced out in TAB1β, and an extra exon, termed exon β, downstream of exons 11 and 12 in the genome was used as the last exon in TAB1β. The mRNA of TAB1β was expressed in all cell lines examined. The TAB1β mRNA encodes a protein with an identical sequence to TAB1 except the C-terminal 69 amino acids were replaced with an unrelated 27-amino acid sequence. Similar to TAB1, TAB1β interacts with p38α but not other MAPKs

and stimulates p38α autoactivation. Different from TAB1, TAB1β does not **bind** or activate **TAK1**. Inhibition of **TAB1**β expression with RNA interference in MDA231 breast cancer cells resulted in the reduction of basal activity of p38α and invasiveness of MDA231 cells, suggesting that TAB1β is involved in regulating p38α activity in physiological conditions.

L2 ANSWER 7 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:118999 CAPLUS
DN 139:33778
TI TAB2 is essential for prevention of apoptosis in fetal liver but not for interleukin-1 signaling
AU Sanjo, Hideki; Takeda, Kiyoshi; Tsujimura, Tohru; Ninomiya-Tsuji, Jun; Matsumoto, Kunihiro; Akira, Shizuo
CS Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Osaka, 565-0871, Japan
SO Molecular and Cellular Biology (2003), 23(4), 1231-1238
CODEN: MCEBD4; ISSN: 0270-7306
PB American Society for Microbiology
DT Journal
LA English
AB The proinflammatory cytokine interleukin-1 (IL-1) transmits a signal via several critical cytoplasmic proteins such as MyD88, IRAKs and TRAF6. Recently, serine/threonine kinase TAK1 and TAK1 binding protein 1 and 2 (TAB1/2) have been identified as mols. involved in IL-1-induced TRAF6-mediated activation of AP-1 and NF-κB via mitogen-activated protein (MAP) kinases and IκB kinases, resp. However, their physiol. functions remain to be clarified. To elucidate their roles in vivo, we generated TAB2-deficient mice. The TAB2 deficiency was embryonic lethal due to liver degeneration and apoptosis. This phenotype was similar to that of NF-κB p65-, IKKβ-, and NEMO/IKKγ-deficient mice. However, the IL-1-induced activation of NF-κB and MAP kinases was not impaired in TAB2-deficient embryonic fibroblasts. These findings demonstrate that TAB2 is essential for embryonic development through prevention of liver apoptosis but not for the IL-1 receptor-mediated signaling pathway.
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L2 ANSWER 8 OF 28 MEDLINE on STN DUPLICATE 2
AN 2003330295 MEDLINE
DN PubMed ID: 12859960
TI A dominant negative TAK1 inhibits cellular fibrotic responses induced by TGF-beta.
AU Ono Koichiro; Ohtomo Toshihiko; Ninomiya-Tsuji Jun; Tsuchiya Masayuki
CS Chugai Pharmaceutical Co., Ltd., Fuji-Gotemba Research Laboratories, Gotemba-shi, Shizuoka-ken, Japan.. onokui@chugai-pharm.co.jp
SO Biochemical and biophysical research communications, (2003 Jul 25) 307 (2) 332-7.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200309
ED Entered STN: 20030716
Last Updated on STN: 20030917
Entered Medline: 20030916
AB Transforming growth factor-beta (TGF-beta) is crucially virulent in the progression of fibrotic disorders. TAK1 (TGF-beta activated kinase 1) is one of the mitogen-activated kinase kinase kinase (MAPKKK) that is involved in TGF-beta signal transduction. To elucidate the importance of TAK1 in TGF-beta-induced fibrotic marker expression, we investigated whether dominant negative TAK1 could suppress TGF-beta signaling. Based

on the finding that **TAB1** (**TAK1 binding** protein 1) **binding** to TAK1 is required for TAK1 activation, a minimal portion of TAK1 lacking kinase activity that binds to TAB1 was designed as a TAK1 dominant negative inhibitor (TAK1-DN). The effect of TAK1-DN was assessed in the cells that respond to TGF-beta stimulation and that lead to the increase in production of extracellular matrix (ECM) proteins. TAK1-DN, indeed, decreased the ECM protein production, indicating that TAK1-DN retains the ability to intercept the TGF-beta signaling effectively.

L2 ANSWER 9 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:810747 CAPLUS
DN 139:378409
TI TAK1-mediated induction of nitric oxide synthase gene expression in glial cells
AU Bhat, Narayan R.; Shen, Qin; Fan, Fan
CS Department of Neurology, Medical University of South Carolina, Charleston, SC, USA
SO Journal of Neurochemistry (2003), 87(1), 238-247
CODEN: JONRA9; ISSN: 0022-3042
PB Blackwell Publishing Ltd.
DT Journal
LA English
AB Inflammatory cell signaling leading to transcriptional activation is primarily mediated by signal transduction via mitogen-activated protein kinase (MAPK) and NFκB pathways. A common upstream kinase that signals the activation of these pathways is TGFβ-activated kinase 1 (TAK1), which itself becomes activated in response to cytokines and upon engagement of a class of cell surface receptors involved in innate immunity, that is Toll-like receptors (TLRs) by bacterial and viral pathogens. This study directly tests the role of TAK1 in the induction of inducible nitric oxide (NO) synthase (iNOS) in glial cells, which represent immune-regulatory cells of the CNS, by transient transfection assays. Transfection of C-6 glia, primary astrocytes and a rat microglial cell line with TAK1 (but not its inactive form) along with its activator protein, TAK1-binding protein 1 (TAB1) resulted in a marked stimulation of a co-transfected rat iNOS promoter-reporter construct (iNOS-Luc). TAK1-induced iNOS-Luc activity was substantially inhibited by pharmacol. inhibitors of the known down-stream kinases, p38 MAPK and JNK (SB203580 and SP620125), and was almost completely blocked by co-expression of a phosphorylation mutant of IκB. TAK1/TAB1 also induced the production of NO and the expression of iNOS in microglial cells in a p38 MAPK-, JNK- and NFκB-dependent manner. The results of these studies provide evidence for an important role for TAK1-mediated intracellular signaling, via p38 MAPK, JNK and NFκB, in the transcriptional activation of iNOS in glial cells.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 28 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:187409 BIOSIS
DN PREV200200187409
TI MAPKK-independent activation of p38alpha mediated by TAB1-dependent autophosphorylation of p38alpha.
AU Ge, Baoxue; Gram, Hermann; Di Padova, Franco; Huang, Betty; New, Liguo; Ulevitch, Richard J.; Luo, Ying; Han, Jiahuai [Reprint author]
CS Department of Immunology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA, 92037, USA
jhan@scripps.edu
SO Science (Washington D C), (15 February, 2002) Vol. 295, No. 5558, pp. 1291-1294. print.
CODEN: SCIEAS. ISSN: 0036-8075.
DT Article

LA English
ED Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002
AB Phosphorylation of mitogen-activated protein kinases (MAPKs) on specific tyrosine and threonine sites by MAP kinase kinases (MAPKKs) is thought to be the sole activation mechanism. Here, we report an unexpected activation mechanism for p38alpha MAPK that does not involve the prototypic kinase cascade. Rather it depends on interaction of p38alpha with TAB1 (transforming growth factor-beta-activated protein kinase 1 (TAK1)-binding protein 1) leading to autophosphorylation and activation of p38alpha. We detected formation of a TRAF6-TAB1-p38alpha complex and showed stimulus-specific TAB1-dependent and TAB1-independent p38alpha activation. These findings suggest that alternative activation pathways contribute to the biological responses of p38alpha to various stimuli.

L2 ANSWER 11 OF 28 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:342890 BIOSIS
DN PREV200200342890
TI Characterization of genes downregulated as a consequence of protein kinase C (PKC) inhibition in chronic lymphocytic leukemia (CLL) by cDNA microchip analysis.
AU Huang, Q. [Reprint author]; Alkan, S. [Reprint author]
CS Loyola University Medical Center, Maywood, IL, USA
SO Laboratory Investigation, (January, 2002) Vol. 82, No. 1, pp. 245A. print.
Meeting Info.: Annual Meeting of the United States and Canadian Academy of Pathology. Chicago, IL, USA. February 23-March 01, 2002.
CODEN: LAINAW. ISSN: 0023-6837.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 19 Jun 2002
Last Updated on STN: 19 Jun 2002

L2 ANSWER 12 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:845431 CAPLUS
DN 136:117124
TI IRAK-mediated translocation of TRAF6 and TAB2 in the interleukin-1-induced activation of NFκB
AU Qian, Youcun; Commane, Mairead; Ninomiya-Tsuji, Jun; Matsumoto, Kunihiro; Li, Xiaoxia
CS Department of Immunology, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, 44195, USA
SO Journal of Biological Chemistry (2001), 276(45), 41661-41667
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The interleukin-1 (IL-1) receptor-associated kinase (IRAK) is required for the IL-1-induced activation of nuclear factor κB and c-Jun N-terminal kinase. The goal of this study was to understand how IRAK activates the intermediate proteins TRAF6, TAK1, TAB1, and TAB2. When IRAK is phosphorylated in response to IL-1, it binds to the membrane where it forms a complex with TRAF6; TRAF6 then dissocs. and translocates to the cytosol. The membrane-bound IRAK similarly mediates the IL-1-induced translocation of TAB2 from the membrane to the cytosol. Different regions of IRAK are required for the translocation of TAB2 and TRAF6, suggesting that IRAK mediates the translocation of each protein sep. The translocation of TAB2 and TRAF6 is needed to form a TRAF6-TAK1-TAB1-TAB2 complex in the cytosol and thus activate TAK1. Our results show that IRAK is required for the IL-1-induced phosphorylation of TAK1, TAB1, and TAB2. The phosphorylation of these three proteins correlates strongly with the activation of nuclear factor κB but is not necessary to activate c-Jun N-terminal kinase.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 28 MEDLINE on STN DUPLICATE 3
AN 2001362568 MEDLINE
DN PubMed ID: 11323434
TI An evolutionarily conserved motif in the TAB1 C-terminal region is necessary for interaction with and activation of TAK1 MAPKKK.
AU Ono K; Ohtomo T; Sato S; Sugamata Y; Suzuki M; Hisamoto N; Ninomiya-Tsuji J; Tsuchiya M; Matsumoto K
CS Chugai Pharmaceutical Co., Ltd., Fuji-Gotemba Research Laboratories, Shizuoka 412-8513, Japan.
SO Journal of biological chemistry, (2001 Jun 29) 276 (26) 24396-400.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010820
Last Updated on STN: 20030105
Entered Medline: 20010816
AB TAK1, a member of the MAPKKK family, is involved in the intracellular signaling pathways mediated by transforming growth factor beta, interleukin 1, and Wnt. TAK1 kinase activity is specifically activated by the **TAK1-binding** protein **TAB1**. The C-terminal 68-amino acid sequence of TAB1 (TAB1-C68) is sufficient for TAK1 interaction and activation. Analysis of various truncated versions of TAB1-C68 defined a C-terminal 30-amino acid sequence (TAB1-C30) necessary for TAK1 binding and activation. NMR studies revealed that the TAB1-C30 region has a unique alpha-helical structure. We identified a conserved sequence motif, PYVDXA/TXF, in the C-terminal domain of mammalian TAB1, Xenopus TAB1, and its Caenorhabditis elegans homolog TAP-1, suggesting that this motif constitutes a specific TAK1 docking site. Alanine substitution mutagenesis showed that TAB1 Phe-484, located in the conserved motif, is crucial for TAK1 binding and activation. The C. elegans homolog of TAB1, TAP-1, was able to interact with and activate the C. elegans homolog of TAK1, MOM-4. However, the site in TAP-1 corresponding to Phe-484 of TAB1 is an alanine residue (Ala-364), and changing this residue to Phe abrogates the ability of TAP-1 to interact with and activate MOM-4. These results suggest that the Phe or Ala residue within the conserved motif of the TAB1-related proteins is important for interaction with and activation of specific TAK1 MAPKKK family members in vivo.

L2 ANSWER 14 OF 28 MEDLINE on STN DUPLICATE 4
AN 2001269992 MEDLINE
DN PubMed ID: 11050078
TI The MAPK kinase kinase TAK1 plays a central role in coupling the interleukin-1 receptor to both transcriptional and RNA-targeted mechanisms of gene regulation.
AU Holtmann H; Enninga J; Kalble S; Thiefes A; Dorrie A; Broemer M; Winzen R; Wilhelm A; Ninomiya-Tsuji J; Matsumoto K; Resch K; Kracht M
CS Institute of Pharmacology, Medical School Hannover, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany.
SO Journal of biological chemistry, (2001 Feb 2) 276 (5) 3508-16.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200106
ED Entered STN: 20010625
Last Updated on STN: 20030105

Entered Medline: 20010621

AB Mechanisms of fulminant gene induction during an inflammatory response were investigated using expression of the chemoattractant cytokine interleukin-8 (IL-8) as a model. Recently we found that coordinate activation of NF-kappaB and c-Jun N-terminal protein kinase (JNK) is required for strong IL-8 transcription, whereas the p38 MAP kinase (MAPK) pathway stabilizes the IL-8 mRNA. It is unclear how these pathways are coupled to the receptor for IL-1, an important physiological inducer of IL-8. Expression of the MAP kinase kinase kinase (MAPKKK) TAK1 together with its coactivator TAB1 in HeLa cells activated all three pathways and was sufficient to induce IL-8 formation, NF-kappaB + JNK2-mediated transcription from a minimal IL-8 promoter, and p38 MAPK-mediated stabilization of a reporter mRNA containing IL-8-derived regulatory mRNA sequences. Expression of a kinase-inactive mutant of TAK1 largely blocked IL-1-induced transcription and mRNA stabilization, as well as formation of endogenous IL-8. Truncated **TAB1**, lacking the **TAK1 binding** domain, or a TAK1-derived peptide containing a TAK1 autoinhibitory domain were also efficient in inhibition. These data indicate that the previously described three-pathway model of IL-8 induction is operative in response to a physiological stimulus, IL-1, and that the MAPKKK TAK1 couples the IL-1 receptor to both transcriptional and RNA-targeted mechanisms mediated by the three pathways.

L2 ANSWER 15 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:278128 CAPLUS
DN 132:320956
TI Method for screening compound inhibiting signal transduction of inflammatory cytokine
IN Tsuchiya, Masayuki; Ohtomo, Toshihiko; Sugamata, Yasuhiro; Matsumoto, Kunihiro
PA Chugai Seiyaku K. K., Japan
SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000023610	A1	20000427	WO 1999-JP5817	19991021
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9962278	A1	20000508	AU 1999-62278	19991021
	EP 1127944	A1	20010829	EP 1999-949347	19991021
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	JP 1998-299962	A	19981021		
	WO 1999-JP5817	W	19991021		

AB By inhibiting the signal transduction of TAK1, effects of inflammatory cytokines are depressed, the production of inflammatory cytokines (IL-1, TNF, etc.) induced by inflammatory stimulus is depressed and the production of other inflammatory cytokines (IL-6, etc.) induced by the inflammatory cytokines is depressed. The assay comprises contacting **TAK1** and **TAB1** (**TAK1** kinase **binding** protein 1) with the sample, monitoring formation of TAK1 kinase-TAB1 complexes, and screening compound that inhibits **TAK1-TAB1 binding**. The method may also use labeled anti-TAB1 antibody for drug screening.

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 16 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:412755 CAPLUS
DN 133:130267
TI BMP2-induced apoptosis is mediated by activation of the TAK1-p38 kinase pathway that is negatively regulated by Smad6
AU Kimura, Naoki; Matsuo, Ritsuko; Shibuya, Hiroshi; Nakashima, Kinichi; Taga, Tetsuya
CS Department of Molecular Cell Biology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan
SO Journal of Biological Chemistry (2000), 275(23), 17647-17652
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Bone morphogenetic protein 2 (BMP2), a member of the transforming growth factor-beta (TGF-β) superfamily, regulates a variety of cell fates and functions. At present, the mol. mechanism by which BMP2 induces apoptosis has not been fully elucidated. Here we propose a BMP2 signaling pathway that mediates apoptosis in mouse hybridoma MH60 cells whose growth is interleukin-6 (IL-6)-dependent. BMP2 dose-dependently induces apoptosis in MH60 cells even in the presence of IL-6. BMP2 has no inhibitory effect on the IL-6-induced tyrosine phosphorylation of STAT3, and the bcl-2 gene expression which is known to be regulated by STAT3, suggesting that BMP2-induced apoptosis is not attributed to alteration of the IL-6-mediated bcl-2 pathway. We demonstrate that BMP2 induces activation of TGF-β-activated kinase (TAK1) and subsequent phosphorylation of p38 stress-activated protein kinase. In addition, forced expression of kinase-neg. TAK1 in MH60 cells blocks BMP2-induced apoptosis. These results indicate that BMP2-induced apoptosis is mediated through the TAK1-p38 pathway in MH60 cells. We also show that MH60-derived transfectants expressing Smad6 are resistant to the apoptotic signal of BMP2. Interestingly, this ectopic expression of Smad6 blocks BMP2-induced TAK1 activation and p38 phosphorylation. Moreover, Smad6 can directly bind to TAK1. These findings suggest that Smad6 is likely to function as a neg. regulator of the TAK1 pathway in the BMP2 signaling, in addition to the previously reported Smad pathway.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 17 OF 28 MEDLINE on STN DUPLICATE 5
AN 2000167218 MEDLINE
DN PubMed ID: 10702308
TI TAK1 mitogen-activated protein kinase kinase kinase is activated by autophosphorylation within its activation loop.
AU Kishimoto K; Matsumoto K; Ninomiya-Tsuji J
CS Department of Molecular Biology, Graduate School of Science, Nagoya University and CREST, Japan Science and Technology Corporation, Chikusa-ku, Nagoya 464-8602, Japan.
SO Journal of biological chemistry, (2000 Mar 10) 275 (10) 7359-64.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200004
ED Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403
AB TAK1, a member of the mitogen-activated kinase kinase kinase family, is activated in vivo by various cytokines, including interleukin-1 (IL-1), or when ectopically expressed together with the **TAK1-binding** protein **TAB1**. However, this molecular mechanism

of activation is not yet understood. We show here that endogenous TAK1 is constitutively associated with TAB1 and phosphorylated following IL-1 stimulation. Furthermore, TAK1 is constitutively phosphorylated when ectopically overexpressed with TAB1. In both cases, dephosphorylation of TAK1 renders it inactive, but it can be reactivated by preincubation with ATP. A mutant of TAK1 that lacks kinase activity is not phosphorylated either following IL-1 treatment or when coexpressed with TAB1, indicating that TAK1 phosphorylation is due to autophosphorylation. Furthermore, mutation to alanine of a conserved serine residue (Ser-192) in the activation loop between kinase domains VII and VIII abolishes both phosphorylation and activation of TAK1. These results suggest that IL-1 and ectopic expression of TAB1 both activate TAK1 via autophosphorylation of Ser-192.

L2 ANSWER 18 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:256102 CAPLUS
DN 134:264947
TI Functional analysis of apoptosis signal-regulating kinase 1 (ASK 1)-binding proteins
AU Mochida, Yoshiyuki
CS Maxillofacial Surg., Maxillofacial Reconstruction Function., Div. Maxillofacial Neck Reconstruction, Grad. Sch., Tokyo Med. Dent. Univ., Japan
SO Kokubyo Gakkai Zasshi (2000), 67(2), 182-192
CODEN: KOGZA9; ISSN: 0300-9149
PB Kokubyo Gakkai
DT Journal
LA Japanese
AB Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are pleiotropic cytokines that activate two transcription factors, Activator Protein-1 (AP-1) and Nuclear Factor-κB (NF-κB). Apoptosis signal-regulating kinase 1 (ASK 1) is a mitogen-activated protein (MAP) kinase kinase kinase (MAPKKK) that is activated by TNF and IL-1, and stimulates c-Jun N-terminal kinase (JNK also known as SAPK; stress-activated protein kinase) and p38 activation. Through genetic screening for ASK 1-binding proteins, Transforming Growth Factor β (TGF-β)-activated kinase (TAK1), another MAPKKK family protein, was identified. Here we report that ASK 1 binds to TAK 1 and dissocs. TAK 1 from TNF receptor-associated factor 6 (TRAF 6), and inhibits TAK 1- and TRAF 6-, but not NFκB-inducing kinase (NIK)-induced NF-κB activation.

L2 ANSWER 19 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:511259 CAPLUS
DN 131:141477
TI NF-κB activation inhibitors, methods for screening the inhibitors using the function of TGF-β activated kinase 1 as parameter, and therapeutical use of the inhibitors for autoimmune diseases and inflammation
IN Sugita, Takahisa; Sakurai, Hiroaki; Kageyama, Noriko; Hasegawa, Ko
PA Tanabe Seiyaku Co., Ltd., Japan
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9940202	A1	19990812	WO 1999-JP422	19990202

W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	AU 9920764	A1	19990823	AU 1999-20764	19990202
	JP 2000197500	A2	20000718	JP 1999-26803	19990204
PRAI	JP 1998-26003	A	19980206		
	JP 1998-309316	A	19981030		
	WO 1999-JP422	W	19990202		

AB Described is a method of identifying nuclear factor κB (NF-κB) activation inhibitors, which have prophylactic and therapeutic uses for autoimmune diseases and inflammation, by testing whether a sample substance is able to inhibit the function of TGF-β activated kinase 1 (TAK1). The function of TAK1 is selected from (1) interaction between TAK1 and TAK1-binding protein 1 (TAB1); (2) protein kinase activity of TAK1; (3) TAK1-mediated intracellular activation of the IκB kinase (IKK) complex; and (4) TAK1-mediated NF-κB activation. The method was demonstrated using a yeast two-hybrid system (using the TAK1-TAB1 interaction as a marker and β-galactosidase a reporter).

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 20 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:286157 CAPLUS
DN 130:334998
TI Method of screening TGF-β inhibitory substances
IN Ono, Koichiro; Ohtomo, Toshihiko; Tsuchiya, Masayuki
PA Chugai Seiyaku Kabushiki Kaisha, Japan
SO PCT Int. Appl., 195 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9921010	A1	19990429	WO 1998-JP4796	19981022
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2306778	AA	19990429	CA 1998-2306778	19981022
	AU 9896468	A1	19990510	AU 1998-96468	19981022
	AU 752461	B2	20020919		
	EP 1043586	A1	20001011	EP 1998-950354	19981022
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 3480941	B2	20031222	JP 1999-523715	19981022
	US 6451617	B1	20020917	US 2000-529279	20000411
	US 2002155624	A1	20021024	US 2002-158895	20020603
	US 6551840	B2	20030422		
	US 2003162228	A1	20030828	US 2003-384743	20030311
PRAI	JP 1997-290188	A	19971022		
	WO 1998-JP4796	W	19981022		
	US 2000-529279	A1	20000411		
	US 2002-158895	A3	20020603		

AB A method of screening substances which inhibit the binding of TGF-β-activated kinase 1 (TAK1) polypeptide to **TAK1-binding** protein (**TAB1**) polypeptide, characterized by contacting TAK1 polypeptide and a sample with TAB1 polypeptide and detecting or determining the TAK1 polypeptide bonded to the TAB1 polypeptide. TAK1 and TAB1 polypeptides may be fusion proteins and may be labeled with radioisotope, enzyme or fluorescent substance for the screening assay.

The TGF-β inhibitor is TGF-β signal transduction inhibitor, extracellular matrix protein production inhibitor, cell proliferation inhibitor, monocyte migration inhibitor, physiol. active substance induction inhibitor, immunosuppression inhibitor, or amyloid β protein precipitation inhibitor. Thus, human TAK1-6xHis, human TAB1-FLAG, and human MBP-TAB1C-FLAG fusion proteins were prepared, purified, and used together with anti-FLAG antibody in an ELISA.

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:752266 CAPLUS
DN 132:10515
TI Substances which inhibit binding of specific proteins to XIAP, screening of them, and their use as drugs
IN Matsumoto, Kunihiro
PA Japan
SO Jpn. Kokai Tokkyo Koho, 43 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 11326328	A2	19991126	JP 1998-130378	19980513
PRAI JP 1998-130378		19980513		

AB Substances which inhibit **binding** of **TAB1** [**TAK1 binding** protein 1 (TAK1: TGF-β-activated kinase 1)], TGF-β type I receptor (TβR-I), or TGF-β type II receptor (TβR-II) to XIAP (X-linked inhibitor of apoptosis protein) are screened by examining whether or not XIAP binds to them when XIAP are contacted with TAB1, TβR-I, or TβR-II and a sample to be tested. XIAP binding is examined by detecting TAB1 or XIAP-mediated biol. activity of TGF-β, e.g. change in expression of reporter genes, e.g. for PAI-1, fibronectin, and type I and IV collagens. The substances inhibit or activate the biol. phenomena, e.g. acceleration of extracellular matrix protein production, cell proliferation inhibition, monocyte migration, bioactive substance induction, immunosuppression, and β-amyloid deposition, through blocking TGF-β signaling, and are useful for treatment of liver fibrosis, lung fibrosis, glomerulonephritis, diabetic nephropathy, nephrosclerosis, vascular restenosis, keloid, scleroderma, autoimmune diseases, and Alzheimer disease. Cloning of some XIAP proteins (IAP family) functioning upstream of TAB1-TAK1 using yeast two-hybrid system, binding specificity of TAB1 to XIAP, interaction interaction between XIAP and TGF-β type I and II receptors, and effect of XIAP on TGF-β signaling were shown.

L2 ANSWER 22 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:712337 CAPLUS
DN 131:317866
TI Functional role for TAB1-TAK1 in TGF-β signaling
AU Shibuya, Hiroshi
CS Div. Morphogenesis, Natl. Inst. Basic Biol., Nishigonaka 38, Myodaiji, Okazaki, 444-8585, Japan
SO Seikagaku (1999), 71(10), 1205-1212
CODEN: SEIKAQ; ISSN: 0037-1017
PB Nippon Seikagakkai
DT Journal; General Review
LA Japanese
AB A review with 13 refs., on roles of TAB1-TAK1, involved in the TGF-β/BMP signaling pathway, in the Xenopus embryogenesis, discussing functions of TAB1-TAK1 in TGF-β signaling pathway, roles of TAB1 and TAK1 in the early development, and regulation of TAB1-TAK1-mediated apoptotic signals by XIAP, a member of inhibitor of apoptosis protein

family.

L2 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:70922 CAPLUS
DN 130:205530
TI XIAP, a cellular member of the inhibitor of apoptosis protein family, links the receptors to TAB1-TAK1 in the BMP signaling pathway
AU Yamaguchi, Kyoko; Nagai, Shin-Ichi; Ninomiya-Tsuji, Jun; Nishita, Michiru; Tamai, Katsuyuki; Irie, Kenji; Ueno, Naoto; Nishida, Eisuke; Shibuya, Hiroshi; Matsumoto, Kunihiro
CS Department of Molecular Biology, Graduate School of Science, Nagoya University, Nagoya, 464-01, Japan
SO EMBO Journal (1999), 18(1), 179-187
CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
AB Signals elicited by transforming growth factor-β (TGF-β) superfamily ligands are generated following the formation of heteromeric receptor complexes consisting of type I and type II receptors. TAK1, a member of the MAP kinase kinase kinase family, and its activator, TAB1, participate in the bone morphogenetic protein (BMP) signaling pathway involved in mesoderm induction and patterning in early Xenopus embryos. However, the events leading from receptor activation to TAK1 activation remain to be identified. A yeast interaction screen was used to search for proteins that function in the pathway linking the receptors and TAB1-TAK1. The human X-chromosome-linked inhibitor of apoptosis protein (XIAP) was isolated as a TAB1-binding protein. XIAP associated not only with TAB1 but also with the BMP receptors in mammalian cells. Injection of XIAP mRNA into dorsal blastomeres enhanced the ventralization of Xenopus embryos in a TAB1-TAK1-dependent manner. Furthermore, a truncated form of XIAP lacking the TAB1-binding domain partially blocked the expression of ventral mesodermal marker genes induced by a constitutively active BMP type I receptor. These results suggest that XIAP participates in the BMP signaling pathway as a pos. regulator linking the BMP receptors and TAB1-TAK1.
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:168877 CAPLUS
DN 128:306472
TI Role of TAK1 and TAB1 in BMP signaling in early Xenopus development
AU Shibuya, Hiroshi; Iwata, Hiroshi; Masuyama, Norihisa; Gotoh, Yukiko; Yamaguchi, Kyoko; Irie, Kenji; Matsumoto, Kunihiro; Nishida, Eisuke; Ueno, Naoto
CS Division of Morphogenesis, Department of Developmental Biology, National Institute for Basic Biology, Okazaki, 444, Japan
SO EMBO Journal (1998), 17(4), 1019-1028
CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
AB Transforming growth factor-β (TGF-β) superfamily members elicit signals through stimulation of serine/threonine kinase receptors. Recent studies of this signaling pathway have identified two types of novel mediating mols., the Smads and TGF-β activated kinase 1 (TAK1). Smads were shown to mimic the effects of bone morphogenetic protein (BMP), activin and TGF-β. TAK1 and TAB1 were identified as a MAPKKK and its activator, resp., which might be involved in the up-regulation of TGF-β superfamily-induced gene expression, but their biol. role is poorly understood. Here, the authors have examined the role of TAK1 and TAB1 in the dorsoventral patterning of early Xenopus embryos. Ectopic expression of Xenopus TAK1 (xTAK1) in early embryos induced cell death.

Interestingly, however, concomitant overexpression of bcl-2 with the activated form of xTAK1 or both xTAK1 and xTAB1 in dorsal blastomeres not only rescued the cells but also caused the ventralization of the embryos. In addition, a kinase-neg. form of xTAK1 (xTAK1KN) which is known to inhibit endogenous signaling could partially rescue phenotypes generated by the expression of a constitutively active BMP-2/4 type IA receptor (BMPR-IA). Moreover, xTAK1KN could block the expression of ventral mesoderm marker genes induced by Smad1 or 5. These results thus suggest that xTAK1 and xTAB1 function in the BMP signal transduction pathway in Xenopus embryos in a cooperative manner.

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 25 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:123735 CAPLUS
DN 128:291850
TI TGF-β-activated kinase 1 stimulates NF-κB activation by an NF-κB-inducing kinase-independent mechanism
AU Sakurai, Hiroaki; Shigemori, Noriko; Hasegawa, Ko; Sugita, Takahisa
CS Lead Generation Research Laboratory, Tanabe Seiyaku Co., Ltd., Osaka, 532-0031, Japan
SO Biochemical and Biophysical Research Communications (1998), 243(2), 545-549
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
AB Several mitogen-activated protein kinase kinase kinases (MAPKKKs), including NF-κB-inducing kinase (NIK), play critical roles in NF-κB activation. The authors isolated cDNA for human TGF-β activated kinase 1 (TAK1), a member of the MAPKKK family, and evaluated its ability to stimulate NF-κB activation. Overexpression of TAK1 together with its activator protein, TAK1 binding protein 1 (TAB1), induced the nuclear translocation of NF-κB p50/p65 heterodimer accompanied by the degradation of IκBα and IκBβ, and the expression of κB-dependent reporter gene. A dominant neg. mutant of NIK did not inhibit TAK1-induced NF-κB activation. These results suggest that TAK1 induces NF-κB activation through a novel NIK-independent signaling pathway.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:720160 CAPLUS
DN 128:11258
TI TAB1 protein and its variant and gene structure
IN Matsumoto, Kunihiro; Nishida, Elsuke
PA Ueno, Naoto, Japan; Chugai Seiyaku Kabushiki Kaisha
SO Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 803571	A2	19971029	EP 1997-302808	19970424
	EP 803571	A3	19990728		
	EP 803571	B1	20041124		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 10004976	A2	19980113	JP 1996-300856	19961028
	US 5837819	A	19981117	US 1996-752891	19961120
	US 5989862	A	19991123	US 1998-144178	19980831
	US 6140042	A	20001031	US 1999-406854	19990929

US 2002119525 A1 20020829 US 2002-123427 20020417
PRAI JP 1996-126282 A 19960424
JP 1996-300856 A 19961028
US 1996-752891 A 19961120
US 1999-406854 A3 19990929
US 2000-688701 B3 20001017
AB Claims include the DNA coding for **TAB1** (protein **TAK1** kinase-**binding**) protein having activity which activates factor TAK1 in the TGF-β signaling pathway, and the amino acid sequence of TAB1. TGF-β formation in cells was induced by protein TAB1, TAK1 (kinase), and the combination of TAB1 and TAK1.

L2 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:530982 CAPLUS
DN 125:212786
TI New MAPKKK, TAK1, functions in TGF-β signal transduction
AU Yamaguchi, Kyoko; Shirakabe, Kyoko
CS Sch. Sci., Nagoya Univ., Nagoya, 464-01, Japan
SO Jikken Igaku (1996), 14(13), 1846-1851
CODEN: JIIGEF; ISSN: 0288-5514
PB Yodosha
DT Journal; General Review
LA Japanese
AB A review, with 9 refs., on search for mammalian novel MAPKKK (mitogen-activated protein kinase kinase kinase) by using MAPK (MAP kinase) cascade of yeast and isolation of TAK1 (TGF-β activated kinase 1) as an activating factor for Ste7-P368, effect of TAK1 on expression of PAI-1 gene, activation of TAK1 by stimulation with TGF-β, MAPK cascade by TGF-β stimulation, identification of **TAB1** (**TAK1-binding** protein 1), and role of TAB1 in TGF-β signal transduction.

L2 ANSWER 28 OF 28 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 6
AN 96175505 EMBASE
DN 1996175505
TI TAB1: An activator of the TAK1 MAPKKK in TGF-β signal transduction.
AU Shibuya H.; Yamaguchi K.; Shirakabe K.; Tonegawa A.; Gotoh Y.; Ueno N.; Irie K.; Nishida E.; Matsumoto K.
CS Department of Molecuiar Biology, Faculty of Science Nagoya University, Chikusa-ku,Nagoya 464-01, Japan
SO Science, (1996) 272/5265 (1179-1182).
ISSN: 0036-8075 CODEN: SCIEAS
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB Transforming growth factor-β (TGF-β) regulates many aspects of cellular function. A member of the mitogen-activated protein kinase kinase kinase (MAPKKK) family, TAK1, was previously identified as a mediator in the signaling pathway of TGF-β superfamily members. The yeast two-hybrid system has now revealed two human proteins, termed TAB1 and TAB2 (for TAK1 **binding** protein), that interact with **TAK1** . **TAB1** and TAK1 were co-immunoprecipilated from mammalian cells. Overproduction of TAB1 enhanced activity of the plasminogen activator inhibitor 1 gene promoter, which is regulated by, TGF-β, and increased the kinase activity of TAK1. TAB1 may function as an activator of the TAK1 MAPKKK in TGF-β signal transduction.

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	(tab1 near2 tab1) near4 (bind or binding)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/12/20 14:06
L2	13	(tak1 near2 tab1) near4 (bind or binding)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/12/20 14:06